Case HU/15-21551

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF ANDREAS WERNER SUPERSAXO ET AL
SERIAL NO.: 09/306,006
FILED: JUNE 5, 1999
FOR: USE OF NANODISPERSIONS IN PHARMACEUTICAL END FORMULATIONS

Group Art Unit: 1619

Examiner: S. SHARAREH

DECLARATION UNDER RULE 132

I, Andreas Werner Supersaxo, a citizen of the Swiss Confederation, residing in Baar, Switzerland, hereby declare:

1. That I am a co-inventor of the invention disclosed and claimed in the above identified patent application;
2. That I have been employed by Vesifact AG since January 1, 1998, specializing in research of nano-sized carrier systems for life science products;
3. That I am presently head of R & D, and have held this position since January 1, 1998;
4. That I am engaged in the research and development of nano-sized carrier systems for life science products;
5. That I consider myself an Expert in preparation of drug delivery systems, especially lipid based delivery systems such as liposomes, mixed micelles and microemulsions;
6. That prior to my employment at Vesifact AG, I was an employee of F.Hoffmann-La Roche AG Basel, Switzerland and of Syntex Research, Palo Alto, California, USA;
7. That I received my Ph. D. in pharmaceutics in 1986 at the Swiss Federal Institute of Technology, Department of Physical Pharmacy, Zurich, Switzerland;
8. That I am a named inventor in U.S. Patents Nos.: 5,376,646; 5,470,582; 5,759,827 and 6,030,602, and
9. That I carried out the following preparative Examples (1) – (7).

It has been the object of the tests reported below to compare a nanodispersion containing ethanol according to the invention with a nanodispersion of the same components but containing no ethanol or wherein ethanol has been replaced by propyleneglycol, which component has been recommended in US-6245349.

I. Comparative Test

The following dispersions were made according to the method described in example 8 of the present application:

Dispersion 1a (corresponding to the invention):

Component	Amount (wt.-%)
Ceramide 3B	0,15
Lipoid S100	1,70
Ethanol (abs.)	1,40
Miglyol 812	3,40
Simusol 98 (HLB: 15,3)	3,35
aq. Phosphate buffer pH 6,0 (10 mM)	90,00

Dispersion 1b (comparison: ethanol replaced by propylene glycol):

Component	Amount (wt.-%)
Ceramide 3B	0,15
Lipoid S100	1,70
Propylenglycol	1,40
Miglyol 812	3,40
Simusol 98 (HLB: 15,3)	3,35
aq. Phosphate buffer pH 6,0 (10 mM)	90,00

Dispersion 1c (comparison: no ethanol):

Component	Amount (wt.-%)
Ceramide 3B	0,15
Lipoid S100	1,70
Miglyol 812	3,40
Simusol 98 (HLB: 15,3)	3,35
aq. Phosphate buffer pH 6,0 (10 mM)	91,40

Dispersion 2a (corresponding to the invention):

Component	Amount (wt.-%)
Ceramide 3B	0,15
Lipoid S100	1,70
Ethanol (abs.)	1,40
Miglyol 812	3,40
Aqualose W20 (HLB: 16)	3,35
aq. Phosphate buffer pH 6,0 (10 mM)	90,00

Dispersion 2b (comparison: ethanol replaced by propylene glycol):

Component	Amount (wt.-%)
Ceramide 3B	0,15
Lipoid S100	1,70
Propylenglycol	1,40
Miglyol 812	3,40
Aqualose W20 (HLB: 16)	3,35
aq. Phosphate buffer pH 6,0 (10 mM)	90,00

Dispersion 2c (comparison: no ethanol):

Component	Amount (wt.-%)
Ceramide 3B	0,15
Lipoid S100	1,70
Miglyol 812	3,40
Aqualose W20 (HLB: 16)	3,35
aq. Phosphate buffer pH 6,0 (10 mM)	91,40

Chemical description of components used:

Ceramide 3B:	N-(9-cis-octadecenoyl)-phytosphingosine
Lipoid S100:	soya phospholipide (Lipoid KG, Ludwigshafen/Germany)
Miglyol 812:	caprylic/capric acid triglyceride
Simusol 98:	polyethoxylated fatty alcohol (Oleth-20)
Aqualose W20:	polyethoxylated lanolin (Laneth-20)

Particle sizes of each dispersion are determined by dynamic light scattering (Nicomp® 380 Submicron Particle Sizer, volume weighted Gaussian analysis). Except for sample 2c, all samples had previously been subjected to 0.2 micron filtration. Results are compiled in the following table:

Table: Effect of alcohols on particle size

Sample	Alcohol	Particle Size
1a (invention)	ethanol	18 nm
1b (comparison)	propylene glycol	31 nm
1c (comparison)	none	113 nm
2a (invention)	ethanol	13 nm
2b (comparison)	propylene glycol	34 nm
2c (comparison)	none	133 nm*

* no filtration possible

II. Discussion of Test Results

Addition of an alcohol lowers the particle size. When propylene glycol is replaced by ethanol, a further significant reduction of the particle size is observed.

III. Conclusion

The results presented and discussed in sections I and II above are a further indication that the lipid particle sizes in aqueous dispersions made using certain polyethoxylated emulsifiers are lowered when ethanol rather than a polyhydric alcohol is added.

These results are important because the particle size is one of the factors determining the distribution and efficacy of a drug administered in the dispersion.

These results are surprising because prior art contains no hint that use of ethanol might provide any advantage over the use of a polyhydric alcohol like propylene glycol.

Hence, the results supply evidence that the subject matter claimed in present application is non-obvious in the light of prior art.

I, Andreas Werner Supersaxo, further declare that all statements made herein of personal knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 14th day of January, 2005

Andreas W. Supersaxo

Andreas Werner Supersaxo